REMARKS/ARGUMENTS

Claims 58-63, 69 and 70 are pending in this application.

Applicants acknowledge with appreciation the withdrawal of the rejections under 35 U.S.C. §102, 35 U.S.C. §103 and 35 U.S.C. §112, second paragraph. The remaining rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph are addressed below.

I. Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-63 and 69-70 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 2 of the instant Office Action).

Claims 58-63 and 69-70 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 3 of the instant Office Action).

Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the polypeptides of Claims 58-63 and 69-70 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without any further experimentation.

The gene amplification data disclosed in Example 114 establishes a credible, substantial and specific patentable utility for the PRO213-1 polypeptides.

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the claimed PRO213-1 polypeptides for the reasons previously set forth in Applicants' Responses filed on October 4, 2004, May 23, 2005, and November 18, 2005.

Furthermore, as first discussed in Applicants' Response of October 4, 2004, Applicants rely on the gene amplification data for patentable utility of the PRO213-1 polypeptide, and the gene amplification data for the gene encoding the PRO213-1 polypeptide is clearly disclosed in the instant specification under Example 114. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO213-1 in at least 35 of the lung and colon primary tumors and tumor cell

lines listed in Table 9. Table 9 teaches that the nucleic acids encoding PRO213-1 showed 1.03 to 5.55 ΔCt units which corresponds to $2^{1.03}$ to $2^{5.55}$ - fold amplification or 2.04 to 46.9 - fold amplification in 16 different human primary lung tumors, LT1, LT1a, LT3, LT4, LT6, LT7, LT9, LT11, LT12, LT13, LT15, LT16, LT17, LT19, LT21 and LT22. PRO213-1 also showed 1.18 to 3.79 ΔCt units which corresponds to $2^{1.18}$ to $2^{3.79}$ - fold amplification or 2.27 to 13.8 - fold amplification in 11 different human primary colon tumors, CT2, CT4, CT5, CT6, CT8, CT10, CT12, CT14, CT15, CT16 and CT17. In addition, PRO213-1 showed 1.31 to 2.95 ΔCt units which corresponds to $2^{1.31}$ to $2^{2.95}$ - fold amplification or 2.48 to 7.73 - fold amplification in three different lung cancer cell lines (Calu-1, H441 and H810), and 1.22 to 2.08 ΔCt units which corresponds to $2^{1.22}$ to $2^{2.08}$ - fold amplification or 2.33 to 4.23 - fold amplification in five different colon cancer cell lines (HT29, SW403, LS174T, HCT15 and HCC2998).

Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO213-1 polypeptide is significantly amplified in a significant number of lung and colon tumors. Thus one of ordinary skill in the art would find it credible that PRO213-1 has utility as a diagnostic marker of lung and colon tumors.

A prima facie case of lack of utility has not been established

The Examiner states that while the Examiner "agrees with Applicants that the nucleic acids have utility as a diagnostic of lung cancer, however, the instant invention is drawn to polypeptides encoded by the nucleic acid, and be cause the art teaches that there is not necessarily a correlation between amplified genomic DNA and mRNA, or mRNA and encoded protein, the polypeptides do not have either a specific and substantial asserted utility or a well established utility." (Page 3 of the instant Office Action).

As discussed in Applicants' Response filed May 23, 2005, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **The standard is not absolute certainty.** The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants submit that the references cited by the PTO are either irrelevant, not contrary to

Applicants' arguments, or actually offer support for Applicants' position, as discussed below. Even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true.

The Examiner first refers to the previously cited references by Pennica *et al.* and Gygi *et al.* Applicants respectfully submit that, for the reasons previously set forth in Applicants' Responses filed on October 4, 2004, and May 23, 2005, the teachings of Pennica *et al.* are specific to *WISP* genes, and say nothing about the correlation of gene amplification and protein expression in general. The Examiner acknowledges that "Gygi *et al.* demonstrates that high levels of mRNA generally correlate with high levels of protein and that it appears that there is a general positive correlation between mRNA levels and protein levels." (Page 4 of the instant Office Action). Thus Gygi *et al.* **supports** Applicants' position that there is a positive correlation between the overexpression of mRNA and protein.

The Examiner next refers to the previously cited references by Lian *et al.* and Fessler *et al.* In Lian *et al.*, the authors looked at the mRNA and protein levels of genes in a derived promyelocytic mouse cell-line during differentiation of the cells from a promyelocytic stage of development to mature neutrophils following treatment with retinoic acid. The level of mRNA expression was measured using 3'-end differential display (DD) and oligonucleotide chip array hybridization to examine the expression of genes at 0, 24, 48 and 72 hours after treatment with retinoic acid. Protein levels were qualitatively assessed at 0 and 72 hours after retinoic acid treatment following 2-dimensional gel electrophoresis.

Lian *et al.* report that they were able to identify 28 proteins which they considered differentially expressed (page 521). Of those 28, only 18 had corresponding gene expression information, and only 13 had measurable levels of mRNA expression (page 521, Table 6). The authors then compared the qualitative protein level from the 2-D electrophoresis gel to the corresponding mRNA level, and reported that only 4 genes of the 18 present in the database had expression levels which were consistent with protein levels (page 521, col. 1). The authors note that "[n]one of these was on the list of genes that were differentially expressed significantly (5-fold or greater change by array or 2-fold or greater change by DD)" (page 521; emphasis added). Based on these data, the authors conclude "[f]or protein levels based on estimated intensity of

Coomassie dye staining in 2DE, there was poor correlation between changes in mRNA levels and estimated protein levels" (page 522, col. 2).

The authors themselves admit that there are a number of problems with the data presented in this reference. At page 520 of this article, the authors explicitly express their concerns by stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and proteins presented at low level will be missed. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this decreased the sensitivity of detection of minor proteins." (emphasis added). It is known in the art that Coomassie dye stain is a very insensitive method of measuring protein. This suggests that the authors relied on a very insensitive measurement of the proteins studied. The conclusions based on such measurements can hardly be accurate or generally applicable. In particular, the total number of proteins examined by Lian *et al.* was only 50 (page 520, col. 2), as compared to the approximately 7000 genes for which mRNA levels were measured (page 515, col. 1). Thus, the conclusions are based on a very small and atypical set of proteins.

Applicants also emphasize that Applicants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. As discussed above, Lian *et al.* did not take genes which showed significant mRNA changes and check the corresponding protein levels. Instead, the authors looked at a small and unrepresentative number of proteins, and checked the corresponding mRNA levels. Based on the authors' criteria, mRNA levels were significantly changed if they were at least 5-fold different when measured using a microchip array, or 2-fold different when using the more sensitive 3'-end differential display (DD). Of the 28 proteins listed in Table 6, only one has an mRNA level measured by microarray which is differentially expressed according to the authors (spot 7: melanoma X-actin, for which mRNA changed from 2539 to 341.3, and protein changed from 1 to 3). None of the other mRNAs listed in Table 6 show a significant change in expression level when using the criteria established by the authors for the less sensitive microarray technique.

There is also one gene in Table 6 whose expression was measured by the more sensitive technique of DD, and its level increased from a qualitative value of 0 to 2, a more than 2-fold

increase (spot 2: actin, gamma, cytoplasmic). This increase in mRNA was accompanied by a corresponding increase in protein level, from 3 to 6.

Therefore, although the authors characterize the mRNA and protein levels as having a "poor correlation," this does not reflect a lack of a correlation between a change in mRNA level and a corresponding change in protein level. Only two genes meet the authors' criteria for differentially expressed mRNA level, and of those, one apparently shows a corresponding change in protein level and one does not. Thus, there is little basis for the authors' conclusion relied on by the PTO that "it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels (as estimated from 2DE)." (Page 11 of the instant Office Action; emphasis added).

Applicants further submit that Fessler *et al.* is not contrary to Applicants' asserted utility, and actually supports Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. As noted above, Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' asserted utility.

Fessler *et al.* studied changes in neutrophil (PMN) gene transcription and protein expression following lipoplysaccharide (LPS) exposure. In Table VIII, Fessler *et al.* list a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertion that changes in mRNA levels lead to corresponding changes in protein levels, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. In the final 6 instances listed in Table VIII, protein levels changed while mRNA

was noted as "absent." This evidence also has no relevance to Applicants' assertion that changes in mRNA levels causes corresponding changes in protein levels. By virtue of being "absent," it is not possible to tell whether mRNA levels were increased, decreased or remained unchanged in PMN upon contact with LPS. Nothing in these results by Fessler *et al.* suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants' assertions.

The PTO has pointed to Fessler's statement regarding Table VIII that there was "a poor concordance between mRNA transcript and protein expression changes." As is clear from the above discussion, this statement does not relate to a lack of correlation between a change in mRNA levels leading to a change in protein levels, because in 5 of 6 such instances, changes in mRNA and protein levels correlated well. Instead, this statement relates to observations in which protein levels changed when mRNA was either unchanged or "absent." As such, this statement is an observation that in addition to transcriptional activity, LPS also has post-transcriptional and possibly post-translational activity that affect protein levels, an observation which is not contrary to Applicants' assertions. Accordingly, Fessler's results are consistent with Applicants' assertion that a change in mRNA level of for a particular protein generally leads to a corresponding change in the level of the encoded protein, since 5 of 6 genes demonstrated such a correlation.

The Examiner next discusses the previously cited reference by Chen *et al.* Applicants reiterate that, as discussed in their Response filed November 18, 2005, no attempt was made to compare expression levels in normal versus tumor samples, and in fact the authors concede that they had too few normal samples for meaningful analysis (page 310, col. 2). As a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples. The Chen paper does not address the issue of whether increased mRNA levels in the tumor samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumorous versus normal tissue.

Applicants have asserted that an increase in mRNA expression in tumor tissue as compared to normal tissue will, in general, correlate with increased protein expression in the same tumor tissue as compared to normal tissue. Chen *et al.* did not examine the correlation

between increases in mRNA and protein expression in tumor tissue as compared to normal tissue and says nothing about it. Accordingly, the results presented in the Chen paper are not applicable to the application at issue.

The Examiner further cites Anderson *et al.* in support of the assertion that "one of ordinary skill in the art would not assume that if an mRNA were overexpressed, the protein would correspondingly be overexpressed." (Page 11 of the instant Office Action). Applicants respectfully point out that Anderson *et al.* looked at levels of mRNA in the same, non-disease state across different genes, not changes in mRNA levels for a single gene. Thus the conclusions of Anderson *et al.* refer to correlations between constant levels of mRNA and protein in normal liver tissue across different genes, not a correlation between a change in mRNA level and a change in protein level in tumor as compared to normal tissue for the same gene and corresponding protein.

Applicants have asserted that increasing the level of mRNA for a particular gene leads to a corresponding increase for the encoded protein. Anderson *et al.* did not study this issue and says absolutely nothing about it. One cannot look at the level of mRNA across several different genes to investigate whether a change in the level of mRNA for a particular gene leads to a change in the level of protein for that gene. Therefore, Anderson *et al.* is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's rejection of Applicants' asserted utility.

The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica *et al.*, Gygi *et al.*, Lian *et al.*, Fessler *et al.*, Chen *et al.* and Anderson *et al.* papers, do not provide sufficient reasons to doubt the statements by Applicants that PRO213-1 has utility. As discussed above, the law does not require the existence of a "necessary" correlation between gene amplification and mRNA and protein expression levels. According to the authors themselves, the data in the above cited references confirm that there is a general trend between gene amplification and mRNA and protein expression levels, which meets the "more likely than not standard" and show that a positive correlation exists between gene amplification and mRNA and protein expression. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner

contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the mRNA and encoded protein will also be expressed at an elevated level.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed October 4, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

With respect to Ornoft *et al.*, the Examiner asserts that "only abundant proteins were analyzed, and the art indicates that very abundant transcripts correlated with high protein levels." (Page 12 of the instant Office Action). While technical considerations did prevent Ornoft *et al.* from evaluating a larger number of proteins, the ones they did look at showed a clear correlation between mRNA and protein expression levels. As Ornoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

Furthermore, as discussed in Applicants' previous Responses, the levels of amplification for PRO213-1 were **not** "low" but significant, and ranged from 2.04 to 46.9-fold, in 35 different lung and colon tumors. Applicants note that the levels of gene amplification observed by Ornoft *et al.* were relatively low, averaging only 0.3-0.4-fold (page 40, col. 1). In particular, the level of gene amplification associated with expression changes was only around two-fold (see Figure 2), less than the 2.04 to 46.9-fold amplification observed for PRO213-1. Even with these relatively low levels of gene amplification, Ornoft *et al.* found that "**[i]n most cases**, chromosomal gains

detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%)" (page 40, col. 2; emphasis added). The level of correlation between DNA copy number and increased mRNA levels observed by Orntoft *et al.*, from **77-80%**, clearly meets the standard of more likely than not. Orntoft *et al.* also found a "highly significant" correlation between mRNA and protein levels, with the two data sets studied having correlations of 39/40 (**98%**) and 19/26 (**73%**) (pages 42-43).

The Examiner also appears to misunderstand the data presented by Hyman *et al.* The Examiner asserts that the Hyman reference found that "[w]hile almost half 44% of the *highly* amplified genes showed overexpression of transcript, more than half did not. Therefore, form Hyman et al., there is not a more likely chance than not that an amplified gene results in overexpressed transcript." (Page 13 of the instant Office Action). The Examiner's assertion is not consistent with the interpretation Hyman *et al.* themselves place on their data, stating that, "The results illustrate **a considerable influence of copy number on gene expression patterns**." (page 6242. col. 1; emphasis added). In the more detailed discussion of their results, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (***i.e.*, belonged to the global upper 7% of expression ratios**) compared with only 6% for genes with normal copy number." (See page 6242, col. 1; emphasis added). These details make it clear that Hyman *et al.* set a highly restrictive standard for considering a gene to be overexpressed; yet almost half of all highly amplified transcripts met even this highly restrictive standard. Therefore, the analysis performed by Hyman *et al.* clearly shows that it is "more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

With respect to the correlation between mRNA expression and protein expression levels, Applicants emphasize that the opinions expressed in the Polakis Declaration are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding

normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

Furthermore, without acquiescing to the propriety of this rejection, and merely to expedite prosecution in this case, **Applicants present a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B**. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.,* greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[1] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."[2] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner."[3] Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[4] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion

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[1] *In re Rinehart,* 531 F.2d 1084, 189 U.S.P.Q. 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F2d. 1015, 226 U.S.P.Q. 881 (Fed. Cir. 1985).

[2] *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)).

[3] *Id.* at 1583.

[4] Part IIB, 66 Fed. Reg. 1098 (2001).

solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis declaration, this rejection is improper under both the case law and the Utility guidelines.

Both Polakis Declarations (Polakis I and II) are further supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (copy enclosed, herein after Cell 3rd) and (4th ed. 2002) (copy enclosed, herein after Cell 4th). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (Emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (Emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (Emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (copy enclosed) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (copy enclosed). Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA resulted from the upregulated transcription of its mRNA." *Zhigang* at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002) (copy enclosed) states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and non-neoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the

seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the

authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Misrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, *e.g.*, a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, *e.g.*, an increase, generally leads to a corresponding change in the level of protein expression, *e.g.*, an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer support of Applicants' asserted utility by showing that, in general, mRNA expression levels correlate with protein expression levels.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast. Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

Applicants note that the new references submitted in the Information Disclosure Statement focus on the correlation between mRNA expression and protein expression levels, and for the most part do not examine gene amplification. However, those few references that actually looked at gene amplification **did** find a correlation between gene amplification and increased mRNA and protein expression levels.

For example, Bea et al. (Cancer Res. 2001; 61(6):2409-12) (abstract attached in Exhibit 12) investigated gene amplification, mRNA expression, and protein expression of the putative oncogene BMI-1 in human lymphoma samples. The authors found BMI-1 gene amplification in four mantle cell lymphomas (MCLs). Bea et al. report that "[t]he **four tumors with gene amplification showed significantly higher mRNA levels** than other MCLs and NHLs with the BMI-1 gene in germline configuration" (Abstract; emphasis added). Applicants note that the fact that five additional MCLs also showed very high mRNA levels without gene amplification does not disprove Applicants' position, because one of skill in the art would understand that there can be more than one cause of mRNA overexpression. The issue is not whether mRNA overexpression is always, or even typically caused by gene amplification, but rather, whether gene amplification typically leads to overexpression. Bea *et al.* further note that the four MCLS with gene amplification of *BMI-1* "showed significantly higher levels of mRNA **and protein expression** compared with other lymphomas with *BMI-1* in germline configuration" (page 2411, col. 1; emphasis added). Thus Bea *et al.* supports Applicants' assertion that gene amplification is correlated with both increased mRNA and protein expression.

Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "**there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied**" (Abstract). Thus Godbout *et al.* also supports Applicants' assertion that gene amplification is correlated with both increased mRNA and protein expression.

Applicants note that while Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) found increased mRNA and protein expression of cyclin D2 and cyclin D3 in the absence of gene amplification, this result proves only that increased mRNA and protein expression levels can result from causes other than gene amplification. As Applicants do not assert that gene amplification is the only cause of increased mRNA and protein expression levels, this result does not disprove Applicants assertion that that increased gene amplification, in general, is correlated with increased mRNA and protein expression.

In summary, Applicants submit herewith a total of 118 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references, together with the previous Ornoft, Hyman, Pollack and

Hanna references of record, support the assertion that that in general, amplification of a particular gene leads to a corresponding change in the level of expression of the mRNA and encoded protein. These references further support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.*, abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true."

Applicants therefore respectfully request withdrawal of the rejections of Claims 58-63, 69 and 70 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62, 69 and 70 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description for the claimed variant polypeptides having at least 80-99% identity to amino acid residues 35-273 of SEQ ID NO:506, wherein the nucleic acid encoding the polypeptide is amplified in colon or lung tumors.

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of the PRO213-1 polypeptide comprising amino acid residues 35-273 of SEQ ID NO:506. The Examiner acknowledges that polypeptides comprising the sequence set forth in SEQ ID NO:506 meet the written description provision of 35 U.S.C. §112, first paragraph. (Page 20 of the instant Office Action). Thus, the genus of polypeptides with at least 80% sequence identity to amino acid residues 35-273 of SEQ ID NO:506, which possess the functional property that the nucleic acid encoding the polypeptide is amplified in colon or lung tumors, would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

The specification describes methods for the determination of percent identity between two amino acid sequences. (See page 123, line 24 to page 125, line 14). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 9 to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). The specification describes methods for one of ordinary skill in the art to identify polypeptides having at least 80% identity to amino acid residues 35-273 of SEQ ID NO:506 wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. Example 114 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. Thus one of ordinary skill in the art would have understood at the time of filing what was encompassed by the claims.

The Examiner has also relied on *Fiddes v. Baird* (30 U.S.P.Q.2d 1481 at 1483) to assert that one cannot describe what one has not been conceived allegedly because in *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad claim where the specification only provide the bovine sequence. (Page 19 of the instant Office Action).

Applicants respectfully submit that the present application is different from *Fiddes v. Baird*. In *Fiddes v. Baird.*, a common structure features, such as the sequence similarity, was not provided for the claimed genus. In contrast, Claims 58-62 clearly define both common structural features (sharing at least 80%, 85%, 90%, 95%, and 99% sequence identity to a known sequence) and functional limitations (being overexpressed in lung or colon tumor cells) of the claimed genus. Therefore, the holding in *Fiddes v. Baird.* does not apply to the present claims.

The Examiner further asserts that "the skilled artisan cannot envision the detailed chemical structure of an encompassed polypeptide, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation" (Page 19 of the instant Office Action). In support of this assertion, the Examiner cites the cases of *Fiers v. Revel* and *Amgen v. Chugai.*

Applicants submit that *Fiers v. Revel* and *Amgen v. Chugai* addressed conception and the written description requirement in the context of DNA-related inventions. The *Amgen* court held

that conception of a DNA invention "has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated." 927 F.2d 1200 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991), at 1206. The *Fiers* court extended this decision into the written description arena, holding that "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity." *Fiers*, 984 F.2d at 1171. Since the instant claims are directed to polypeptides, *Fiers* and *Amgen* are distinguished on the facts and do not apply.

More recently, in *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard that "the written description requirement can be met by 'showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. While the invention in *Enzo* was still a DNA, the holding has been treated as being applicable to proteins as well. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids.

Accordingly, current applicable case law holds that biological sequences are not adequately described **solely** by a description of their desired functional activities. The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural limitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[5] As discussed above, Applicants have recited structural features, namely, 80% sequence identity to amino acid residues 35-273 of SEQ ID NO:506, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific activity for the encoding nucleic acid,

[5] M.P.E.P. §2163 II(A)(3)(a).

wherein the nucleic acid encoding the polypeptide is amplified in colon or lung tumors. Accordingly, a description of the claimed genus has been achieved.

This particular combination of functional activity and structural homology, as disclosed in the specification, has been recognized by the USPTO as sufficient to describe a claimed genus of polypeptides. The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

As discussed above, the procedures for making the claimed variant polypeptides are well known in the art and described in the specification. The specification also provides an assay, shown in Example 114, for detecting the recited functional activity of the nucleic acids encoding the variant polypeptides. Finally, the claimed variant polypeptides possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, amino acid residues 35-273 of SEQ ID NO:506. Accordingly, the claimed polypeptide variants meet the standards set forth in the Written Description Guidelines.

Applicants therefore respectfully request that the Examiner reconsider and withdraw the written description rejection of Claims 58-62 and 69-70 under 35 U.S.C. §112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Although no fees are due, the Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2630 P1C4**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 7, 2006

By: _____
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